



## Hajdu-Cheney syndrome

Hajdu-Cheney syndrome is a rare disorder that can affect many parts of the body, particularly the bones. Loss of bone tissue from the hands and feet (acro-osteolysis) is a characteristic feature of the condition. The fingers and toes are short and broad, and they may become shorter over time as bone at the tips continues to break down. Bone loss in the fingers can interfere with fine motor skills, such as picking up small objects.

Bone abnormalities throughout the body are common in Hajdu-Cheney syndrome. Affected individuals develop osteoporosis, which causes the bones to be brittle and prone to fracture. Many affected individuals experience breakage (compression fractures) of the spinal bones (vertebrae). Some also develop abnormal curvature of the spine (scoliosis or kyphosis). Hajdu-Cheney syndrome also affects the shape and strength of the long bones in the arms and legs. The abnormalities associated with this condition lead to short stature.

Hajdu-Cheney syndrome also causes abnormalities of the skull bones, including the bones of the face. The shape of the skull is often described as dolichocephalic, which means it is elongated from back to front. In many affected individuals, the bone at the back of the skull bulges outward, causing a bump called a prominent occiput. Distinctive facial features associated with this condition include widely spaced and downward-slanting eyes, eyebrows that grow together in the middle (synophrys), low-set ears, a sunken appearance of the middle of the face (midface hypoplasia), and a large space between the nose and upper lip (a long philtrum). Some affected children are born with an opening in the roof of the mouth called a cleft palate or with a high arched palate. In affected adults, the facial features are often described as "coarse."

Other features of Hajdu-Cheney syndrome found in some affected individuals include joint abnormalities, particularly an unusually large range of joint movement (hypermobility); dental problems; hearing loss; a deep, gravelly voice; excess body hair; recurrent infections in childhood; heart defects; and kidney abnormalities such as the growth of multiple fluid-filled cysts (polycystic kidneys). Some people with this condition have delayed development in childhood, but the delays are usually mild.

The most serious complications of Hajdu-Cheney syndrome, which occur in about half of all affected individuals, are abnormalities known as platybasia and basilar invagination. Platybasia is a flattening of the base of the skull caused by thinning and softening of the skull bones. Basilar invagination occurs when the softened bones allow part of the spine to protrude abnormally through the opening at the bottom of the skull, pushing into the lower parts of the brain. These abnormalities can lead to severe neurological problems, including headaches, abnormal vision and balance, a buildup of fluid in the brain (hydrocephalus), abnormal breathing, and sudden death.

The signs and symptoms of Hajdu-Cheney syndrome vary greatly among affected individuals, even among members of the same family. Many of the disorder's features, such as acro-osteolysis and some of the characteristic facial features, are not present at birth but become apparent in childhood or later. The risk of developing platybasia and basilar invagination also increases over time.

The features of Hajdu-Cheney syndrome overlap significantly with those of a condition called serpentine fibula-polycystic kidney syndrome (SFPKS). Although they used to be considered separate disorders, researchers discovered that the two conditions are associated with mutations in the same gene. Based on these similarities, many researchers now consider Hajdu-Cheney syndrome and SFPKS to be variants of the same condition.

## Frequency

Hajdu-Cheney syndrome is a rare disease; its prevalence is unknown. Fewer than 100 affected individuals have been described in the medical literature.

## Genetic Changes

Hajdu-Cheney syndrome is associated with mutations in the *NOTCH2* gene. This gene provides instructions for making a receptor called Notch2. Receptor proteins have specific sites into which certain other proteins, called ligands, fit like keys into locks. When a ligand binds to the Notch2 receptor, it triggers signals that are important for the normal development and function of many different types of cells. Studies suggest that signaling through the Notch2 receptor is important for the early development of bones and later for bone remodeling, a normal process in which old bone is removed and new bone is created to replace it. Notch2 signaling also appears to be involved in the development of the heart, kidneys, teeth, and other parts of the body.

Mutations in a specific area near the end of the *NOTCH2* gene are associated with Hajdu-Cheney syndrome. These mutations lead to a version of the Notch2 receptor that cannot be broken down normally. As a result, the receptor continues to be active even after signaling should stop. Researchers are unsure how excessive Notch2 signaling is related to the varied features of Hajdu-Cheney syndrome. They suspect that the skeletal features of the disorder, including acro-osteolysis, osteoporosis, and distinctive facial features, likely result from abnormal bone development and remodeling. Excess signaling through the overactive Notch2 receptor may increase the removal of old bone, reduce the formation of new bone, or both. It is less clear how the overactive receptor contributes to the other signs and symptoms of this condition.

## Inheritance Pattern

This condition is inherited in an autosomal dominant pattern, which means one copy of the altered *NOTCH2* gene in each cell is sufficient to cause the disorder. Most cases result from new mutations in the gene and occur in people with no history of the

disorder in their family. Less commonly, an affected person inherits the mutation from one affected parent.

### **Other Names for This Condition**

- acroosteolysis dominant type
- acroosteolysis with osteoporosis and changes in skull and mandible
- arthro-dento-osteo dysplasia
- arthrodentoosteodysplasia
- Cheney syndrome
- cranioskeletal dysplasia with acro-osteolysis
- familial osteodysplasia
- hereditary osteodysplasia with acro-osteolysis
- HJCYS
- serpentine fibula-polycystic kidney syndrome
- SFPKS

### **Diagnosis & Management**

These resources address the diagnosis or management of Hajdu-Cheney syndrome:

- Genetic Testing Registry: Hajdu-Cheney syndrome  
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C0917715/>

These resources from MedlinePlus offer information about the diagnosis and management of various health conditions:

- Diagnostic Tests  
<https://medlineplus.gov/diagnostictests.html>
- Drug Therapy  
<https://medlineplus.gov/drugtherapy.html>
- Surgery and Rehabilitation  
<https://medlineplus.gov/surgeryandrehabilitation.html>
- Genetic Counseling  
<https://medlineplus.gov/geneticcounseling.html>
- Palliative Care  
<https://medlineplus.gov/palliativecare.html>

## **Additional Information & Resources**

### MedlinePlus

- Encyclopedia: Compression Fractures of the Back  
<https://medlineplus.gov/ency/article/000443.htm>
- Encyclopedia: Kyphosis  
<https://medlineplus.gov/ency/article/001240.htm>
- Encyclopedia: Scoliosis  
<https://medlineplus.gov/ency/article/001241.htm>
- Health Topic: Bone Diseases  
<https://medlineplus.gov/bonediseases.html>
- Health Topic: Osteoporosis  
<https://medlineplus.gov/osteoporosis.html>

### Genetic and Rare Diseases Information Center

- Acroosteolysis dominant type  
<https://rarediseases.info.nih.gov/diseases/508/acroosteolysis-dominant-type>

### Additional NIH Resources

- NIH Osteoporosis and Related Bone Diseases National Resource Center  
[https://www.niams.nih.gov/Health\\_Info/Bone/Osteoporosis/](https://www.niams.nih.gov/Health_Info/Bone/Osteoporosis/)

### Educational Resources

- Disease InfoSearch: Acroosteolysis with Osteoporosis and Changes in Skull and Mandible  
<http://www.diseaseinfosearch.org/Acroosteolysis+with+Osteoporosis+and+Changes+in+Skull+and+Mandible/169>
- MalaCards: hajdu-cheney syndrome  
[http://www.malacards.org/card/hajdu\\_cheney\\_syndrome](http://www.malacards.org/card/hajdu_cheney_syndrome)
- Orphanet: Acroosteolysis dominant type  
[http://www.orpha.net/consor/cgi-bin/OC\\_Exp.php?Lng=EN&Expert=955](http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=955)

### Patient Support and Advocacy Resources

- National Organization for Rare Disorders (NORD)  
<https://rarediseases.org/rare-diseases/hajdu-cheney-syndrome/>
- National Osteoporosis Foundation  
<https://www.nof.org/>

### Genetic Testing Registry

- Hajdu-Cheney syndrome  
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C0917715/>

### ClinicalTrials.gov

- ClinicalTrials.gov  
<https://clinicaltrials.gov/ct2/results?cond=%22Hajdu-Cheney+syndrome%22+OR+%22arthro-dento-osteo+dysplasia%22>

### Scientific articles on PubMed

- PubMed  
<https://www.ncbi.nlm.nih.gov/pubmed?term=%28Hajdu-Cheney+syndrome%5BTIAB%5D%29+OR+%28Hajdu-Cheney+syndrome%5BMAJR%5D%29+AND+english%5BIa%5D+AND+human%5Bmh%5D+AND+%22last+3600+days%22%5Bdp%5D>

### OMIM

- HAJDU-CHENEY SYNDROME  
<http://omim.org/entry/102500>

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